# A Matching-Adjusted Indirect Comparison of Sonidegib and Vismodegib in Advanced Basal Cell Carcinoma

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## BACKGROUND

- Basal cell carcinoma (BCC) is one of the most prevalent cancers[1] and is generally diagnosed and treated early.[2] However, in a few cases, BCC can metastasize or progress locally to the extent that curative surgery or radiotherapy is not feasible.[2,3] Advanced BCC can cause disfigurement and morbidity and can decrease patients' quality of life.[3,4]

### Treatment Options

- Based on single-arm trial data (the 200-mg arm of the BOLT trial[5]), sonidegib (Odomzo; Novartis) was approved recently in the United States and European Union to treat adults with locally advanced BCC (laBCC) who are ineligible for curative surgery or radiotherapy.[6,7]
- Vismodegib (Erivedge; Roche), the other approved targeted oral therapy for advanced BCC, also was assessed in a single-arm trial (ERIVANCE).[8] Vismodegib is indicated for the treatment of adults with symptomatic metastatic BCC or adults with laBCC who are ineligible for surgery or radiotherapy.[9,10]

### Comparison of Effectiveness

- In the absence of head-to-head trial data or a common comparator on which a network meta-analysis can be based, an unadjusted ("naïve") comparison of the two treatments can be made; however, in the single-arm trials, differences between the patient characteristics that may be prognostic for the outcomes of interest can confound the comparison.
- Researchers have developed new meta-analytic methods aiming to match the baseline characteristics of patient populations between trials when conducting indirect comparisons. One of these methods is matching-adjusted indirect comparison (MAIC),[11,12] where individual patient data (IPD) from one trial are weighted to match the mean baseline characteristics of the published baseline characteristics from the second trial. Results of the trial with IPD are reanalyzed using the weighted patient-level data set. The MAIC method is designed to reduce confounding of treatment effects by differences between the studies in the patient characteristics used in the matching procedure.

## OBJECTIVE

- To examine the comparative effectiveness of sonidegib and vismodegib in patients with laBCC who are ineligible for curative surgery or radiotherapy using an MAIC (vs. an unadjusted indirect comparison).

## METHODS

- We first undertook a critical review and comparison of the BOLT and ERIVANCE trial designs, outcome definitions, and baseline patient characteristics; conducted a targeted literature review; and consulted with clinical advisors to identify baseline patient characteristics that may be considered prognostic for the outcomes of interest.
- We then specified the parameters to be considered in the analysis.
- Finally, we conducted the MAIC and compared the results to those from an unadjusted indirect comparison.

### Assessment of Trials and Selection of Analysis Parameters

- The BOLT and ERIVANCE studies were assessed to determine the suitability of the clinical trials for conducting an indirect comparison of sonidegib and vismodegib for the treatment of patients with laBCC who are ineligible for curative surgery or radiotherapy (Table 1).

**Table 1. Overview of Trial Designs, Including Outcome Definitions**

| Trial Characteristic | BOLT | ERIVANCE |
|---|---|---|
| Study description | • Multicenter, international, randomized, double-blind, phase 2 study to investigate the safety and efficacy of sonidegib<br>• Patients were randomized to receive either 200 mg or 800 mg of sonidegib[5] | • Single-arm, multicenter, international, nonrandomized, phase 2 study to investigate the safety and efficacy of vismodegib[8] |
| Key inclusion criteria | • Histologically confirmed diagnosis, with measurable disease of ≥ 1 lesion, ≥ 10 mm in at least 1 dimension by magnetic resonance imaging/color photograph<br>• Patients were not amenable to radiation therapy, curative surgery<br>• Patients were not required to have received any prior radiotherapy | • Histologically confirmed diagnosis, with measurable disease of ≥ 1 lesion, ≥ 10 mm in the longest dimension<br>• Patients were considered to be inoperable or medically contraindicated to surgery<br>• Patients were required to have been administered radiotherapy unless radiotherapy was contraindicated or inappropriate |
| Time periods for reported results (minimum duration of follow-up) | • Primary analysis (6 months of follow-up)[13]<br>• 12-month update (12 months of follow-up)[5]<br>• 18-month update (18 months of follow-up)[14] | • Primary analysis (9 months of follow-up)[8]<br>• 6-month update (15 months of follow-up)[15]<br>• 12-month update (21 months of follow-up)[16]<br>• 18-month update (27 months of follow-up)[17]<br>• 24-month update (33 months of follow-up)[18]<br>• 30-month update (39 months of follow-up)[19] |
| Primary efficacy endpoint | • ORR by central review | • ORR by central review |
| Other efficacy and safety outcomes available | • DOR<br>• Complete response rate<br>• PFS<br>• Overall survival<br>• Time to response<br>• Specific adverse events | • DOR<br>• Complete response rate<br>• PFS<br>• Overall survival<br>• Specific adverse events |

DOR = duration of response; ORR = objective response rate; PFS = progression-free survival.

- Any baseline characteristic may provide information relevant to the trial outcomes; however, given the small sample size of the BOLT study (n = 66 for laBCC, 200 mg), there was concern that including all reported baseline variables in the matching procedure would lead to extreme weights and unstable results. Therefore, the number of matching variables was limited to two. To select the matching variables, baseline patient characteristics from BOLT and ERIVANCE were reviewed and evaluated based on the following criteria:
  - Available and presented consistently in both BOLT and ERIVANCE studies
  - Distributed differently across BOLT and ERIVANCE studies (based on visual review)
  - Prognostic for (i.e., predictive of) the efficacy outcomes (as verified and assessed by clinical advisors)
- Table 2 summarizes the candidate MAIC matching variables.
- Based on the review, the parameters for the analyses were selected a priori (Table 3).

**Table 2. Overview of Trial Patient Baseline Characteristics**

| Potential Matching Variable | Available and Presented Consistently in BOLT and ERIVANCE Studies? | Distribution Differs Between BOLT and ERIVANCE? | Is the Variable Prognostic? |
|---|---|---|---|
| Age | Yes | No<br>• BOLT = 64.6 (mean)<br>• ERIVANCE = 61.4 (mean) | Unknown<br>BOLT clinical study report[20] suggests prognostic, but Chang et al.[21] suggest nonsignificant relationship with ORR |
| Sex | Yes | No<br>• BOLT = 57.6% (male)<br>• ERIVANCE = 55.6% (male) | Unknown |
| Prior radiotherapy for BCC | Yes | Yes<br>• BOLT = 7.6%<br>• ERIVANCE = 20.6% for target and 27.0% for current or prior | Unknown<br>Chang et al.[21] suggest nonsignificant relationship with ORR |
| Prior systemic therapy for BCC | Yes | No<br>• BOLT = 6.1%<br>• ERIVANCE = 11.1% (systematic or topical) | Unknown<br>Chang et al.[21] suggest significant relationship with ORR |
| Prior surgery for BCC | Yes | Yes<br>• BOLT = 72.7%<br>• ERIVANCE = 88.9% | Clinical advisors suggest highly prognostic in refractory population |

Note: BOLT summaries are based on the 200-mg primary full analysis set population; ERIVANCE summaries are based on Sekulic et al.[8] and EMA assessment report.[9]

**Table 3. Parameters Selected for Analysis**

| Parameter | Selected for Analyses |
|---|---|
| Time period of reported results (minimum follow-up period) | • BOLT: 18-month update (18 months of follow-up)<br>• ERIVANCE: 12-month update (21 months of follow-up) |
| Efficacy outcomes | • ORR<br>• DOR<br>• PFS |
| Matching variables | • Prior BCC radiotherapy<br>• Prior BCC surgery |

- The BOLT 18-month update (18 months of follow-up) and the ERIVANCE 12-month update (21 months of follow-up) were considered to be closely aligned (see Table 1) and provided the longest common duration of follow-up; therefore, these time points were selected for the analysis.
- ORR was selected as an outcome to be analyzed because it was the primary efficacy endpoint in both trials.
- PFS was selected as an additional outcome because payers are an important audience for comparative effectiveness information, and PFS can facilitate development of a cost-effectiveness model according to best practices in advanced cancer for submission to health technology assessment authorities.
- DOR was selected as an additional outcome because it is considered important by many dermatologists (who also may not be as familiar with typical oncology trial endpoints such as PFS).
- Prior BCC radiotherapy and prior surgery were selected as the two matching variables based on the criteria that the variables are available in both studies, different in their distributions, and expected by clinical advisors to be prognostic.

### Statistical Methods

- All analyses were conducted using SAS statistical software version 9.3 or higher.
- The statistical methodology detailed by Signorovitch et al.[11,12] was implemented for the MAIC analysis.
  - Using this method, patients in the sonidegib study (i.e., for whom IPD data were available) were weighted so that their selected baseline characteristics (proportions) matched the selected aggregate baseline characteristics reported for the published vismodegib study.
  - The Newton-Raphson algorithm was used to obtain the unique solution for the weights (using SAS NLPNRA subroutine and GRD option in PROC IML).
  - After matching, weighted statistical analysis of the key sonidegib study efficacy endpoints was produced. Specifically, a weighted statistical analysis of the sonidegib IPD was applied using SAS via a weighted chi-square test (PROC FREQ) or weighted Kaplan-Meier analysis (PROC LIFETEST).
- Because the small sample size in the trials was a concern, an examination was conducted to identify any extreme weights produced by the MAIC analysis.
- Following the MAIC analysis, a naïve indirect comparison of the selected efficacy endpoints was conducted between the two treatments.

## RESULTS

- Results (95% confidence interval [CI]) from the individual studies for sonidegib and vismodegib were 56.1% (44.1-68.0) and 47.6% (35.5-60.6) for ORR and 22.1 (14.8-not estimable [NE]) months and 9.5 (7.4-14.8) months for median PFS, respectively. After reweighting, the sonidegib values were effectively unchanged: 56.7% (44.7-68.6) for ORR and 22.1 (14.8-NE) months for median PFS (Table 4).
- The matching procedure was effective in that the postmatched BOLT laBCC population had similar proportions of prior BCC radiotherapy and prior BCC surgery compared with the ERIVANCE laBCC population (Table 4).
- The matching-adjusted BOLT patient weights were not extreme (mean weight, 1.00; standard deviation, 0.573; range, 0.40-2.72).
- Other baseline patient characteristics were evaluated postmatch to determine if the MAIC procedure inadvertently caused other baseline patient characteristics to become unbalanced with the prematched values. The unmatched patient characteristics of age, age range, race, Eastern Cooperative Oncology Group (ECOG) status, and sex were compared pre- and postmatch (Table 5). The small change from the unmatched baseline variables strengthens confidence in the MAIC results.

**Table 4. Baseline Characteristics and Efficacy Outcomes**

| | BOLT[a] Sonidegib 200 mg | | ERIVANCE[a] Vismodegib 150 mg (n = 63) |
|---|---|---|---|
| | Prematched (n = 66) | Postmatched (n = 66) | |
| **Matched baseline patient characteristics** | | | |
| Prior BCC radiotherapy<br>Yes, n[b] (%) | 5 (7.6%) | (20.6%) | 13 (20.6%) |
| Prior BCC surgery<br>Yes, n[b] (%) | 48 (72.7%) | (89.0%) | 56 (88.9%) |
| **Efficacy outcomes** | | | |
| ORR, n[b] (%) (95% CI[c]) | 37 (56.1%) (44.1-68.0) | (56.7%) (44.7-68.6) | 30 (47.6%) (35.5-60.6) |
| Median PFS in months (95% CI) | 22.1 (14.8 to NE) | 22.1 (14.8 to NE) | 9.5 (7.4-14.8) |
| Median DOR[d] in months (95% CI) | 14.3 (12.0-20.2) | 15.7 (12.9-23.1) | NE[e] (9.0 to NE) |

[a] BOLT data analysis was based on the 18-month update (i.e., 18 months of patient follow-up); ERIVANCE summary information was based on the 12-month update (i.e., 21 months of patient follow-up).
[b] Postmatched BOLT results were weighted at the person-level; therefore, the number of patients was not available.
[c] BOLT CIs for ORR were based on Wald asymptotic confidence limits (owing to the incorporation of weights). This differed from the main BOLT analysis that used the Clopper-Pearson exact method.
[d] DOR was based on investigator review.
[e] Median DOR based on independent review facility was reported to be 9.5 months (95% CI, 7.4-21.4).

**Table 5. Baseline Characteristics of Unmatched Variables**

| | BOLT[a] Sonidegib 200 mg | | ERIVANCE[a] Vismodegib 150 mg (n = 63) |
|---|---|---|---|
| | Prematched (n = 66) | Postmatched (n = 66) | |
| **Age in years** | | | |
| Mean | 64.6 | 64.6 | 61.4 |
| Median | 67.0 | 67.0 | 62.0 |
| Standard deviation | 15.9 | 15.5 | 16.9 |
| **Age range in years, n[b] (%)** | | | |
| 18-40 | 6 (9.1%) | (8.6%) | 7 (11.1%) |
| 41-64 | 22 (33.3%) | (31.6%) | 26 (41.3%) |
| ≥ 65 | 38 (57.6%) | (59.8%) | 30 (47.6%) |
| **Race, n[b] (%)** | | | |
| White | 59 (89.4%) | (90.8%) | (100.0%) |
| Other | 7 (10.6%) | (9.2%) | (0.0%) |
| **ECOG status, n[b,c] (%)** | | | |
| 0 | 44 (66.7%) | (69.3%) | 48 (76.2%) |
| 1 | 16 (24.2%) | (21.5%) | 13 (20.6%) |
| 2 | 4 (6.1%) | (6.0%) | 2 (3.2%) |
| **Sex, n[b] (%)** | | | |
| Male | 38 (57.6%) | (60.8%) | 35 (55.6%) |
| Female | 28 (42.4%) | (39.2%) | 28 (44.4%) |

[a] BOLT data analysis was based on the 18-month update (i.e., 18 months of patient follow-up); ERIVANCE summary information was based on the 12-month update (i.e., 21 months of patient follow-up).
[b] Postmatched BOLT results were weighted at the person-level; therefore, the number of patients was not available.
[c] Two patients had missing ECOG status at baseline.

## LIMITATIONS

- MAIC adjusts for certain baseline characteristics; however, the indirect comparison is not anchored to a common comparator, because the available data are based on two single-arm trials; therefore, relative effects cannot be examined.
- The use of IPD (from BOLT) and MAIC can reduce differences in the distribution of observed between-study differences in matched variables; however, unobserved differences between the study populations may still result in residual confounding.
- The small size of the BOLT 200-mg laBCC patient group could result in the MAIC relying on extreme weights for some matching variables; to address this possibility, a limited number of matching variables was selected. It is uncertain whether, if different matching variables had been chosen (e.g., age), the results would have been similar to those presented in the current analysis.
- The small size of the BOLT 200-mg laBCC group could result in the MAIC relying on extreme weights for some matching variables; therefore, a limited number of matching variables was selected. It is uncertain whether, if different matching variables had been chosen (e.g., age), the results would have been similar to those presented.

## CONCLUSIONS

**The comparative effectiveness of sonidegib compared with vismodegib remains unchanged (in relation to a naïve comparison) after adjusting BOLT patient-level data to match published ERIVANCE values for baseline prevalence of prior surgery and radiotherapy. The MAIC does not change the overall conclusions from the unadjusted indirect comparison of the two drugs.**

## REFERENCES

Please see handout for complete reference list.

## CONTACT INFORMATION

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Presented at the ISPOR 21st Annual International Meeting, May 21-25, 2016, Washington, DC, United States

This study was sponsored by Novartis Pharmaceuticals Corporation.